The effect of obesity on survival in patients undergoing coronary artery bypass graft surgery receiving a radial artery

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Abstract

Objective(s): The radial artery (RA) is often used as a second arterial conduit in preference to the right internal thoracic artery in obese patients undergoing coronary artery bypass grafting (CABG) to minimise the risk of sternal wound complication. However, obesity has been found to promote RA vasoreactivity and early atherosclerotic degeneration, which may compromises graft patency when used in patients having CABG. Therefore, we investigated the effect of the RA as second conduit, when compared with the saphenous vein (SV) on the long term survival in obese and non-obese patients undergoing first time CABG.

Methods: Propensity score matching was used to adjust for imbalance and the effect of the RA in obese (body mass index, BMI≥30) and non-obese (BMI<30) subjects was tested by means of time segmented Cox regression.

Results: The study population consisted of 12244 patients undergoing first time CABG. Of those, 8740 subjects were non-obese and 3504 obese. The RA was used as second arterial conduit in 1322 (15%) non-obese patients and 685(20%) obese patients. The use of the RA when compared to saphenous vein, reduced the risk of late death in subjects with BMI<30 (HR 0.75;95%CI0.62-0.89;P=0.001) but not in those with BMI≥30 (HR0.88;95%CI0.68-1.13;P=0.3), regardless of their diabetes status (non-diabetic HR 0.87[0.63-1.20] versus diabetics HR 0.83[0.54-1.26];interaction P=0.8).

Conclusion: The use of the RA in preference to SV as second conduit was associated with improved long term survival in non-obese patient undergoing CABG. This benefit was no longer present in obese patients regardless of their diabetes status.

Keywords: coronary artery bypass graft; obesity; arterial graft

Introduction

Worldwide obesity has more than doubled since 1980. In 2014, more than 1.9 billion adults, 18 years and older, were overweight, and 600 million obese. Obesity is a major risk factor for coronary artery disease, the leading cause of death in 2012 [1]. As a consequence the impact of obesity on outcomes after coronary artery bypass graft (CABG) surgery has become a focus of increasing attention [2]. High body mass index (BMI) has been consistently associated with poorer long-term survival [3]. Its detrimental effect has been attributed to the progression of earlier grafts atherosclerosis [4] which leads to a greater risk of clinical events [5].

Arterial grafts when compared with saphenous vein (SV) grafts, would be expected to provide a survival benefit in obese patients due to their reduced susceptibility to atherosclerosis [6]. The right internal thoracic artery as second arterial conduit, has been demonstrated to be associated with survival benefit in obese undergoing CABG [6], however, surgeons continue to be reluctant to use it in this high risk subgroup because of the potential for sternal wound complications [7,8]. This often results in the RA to be preferred as the second conduit of choice in obese patients [9]. However, obesity is associated with chronic systemic inflammation, endothelial dysfunction, renin-angiotensin and sympathetic nervous systems activation [10] which can enhance the RA vasoreactivity and early atherosclerosis [11-14]. In the present study we tested the hypothesis that the survival benefit from the RA over the SV might be reduced in obese when compared to non-obese patients undergoing first time CABG.

Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. We retrospectively analysed prospectively collected data from The National Institute for Cardiovascular Outcomes Research

(NICOR) NACSA registry on 1 June 2015 for all isolated first time CABG procedures performed at the Bristol Heart Institute, Bristol United Kingdom from 1996 to April 2015. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required. Briefly, duplicate records and non-adult cardiac surgery entries were removed; transcriptional discrepancies harmonized; and clinical conflicts and extreme values corrected or removed. The data are returned regularly to the local units for validation.

Further details and definition of variables are available at http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets. Among 12247 isolated first time CABG cases performed during the study period, we selected subjects who met the following criteria: multivessel coronary disease including left main and/or left anterior descending (LAD) coronary disease; requiring at least 2 grafts; CABG performed by using the following strategies: left internal thoracic artery (LITA) grafting and RA as second arterial conduit with or without additional SV grafts (RA group) or LITA grafting with additional SV grafts only (SV group). In the present series, the RA was considered only in case of target stenosis ≥75% and it was used as a free conduit proximally connected to the ascending aorta or as a composite y graft to the LITA. The LITA was used as in-situ to graft the LAD territory. We classified anyone with a BMI of 30 kg/m^2 and higher as obese, in line with the National Heart Lung and Blood Institute classification of obesity.

End-points

Primary end point was all-cause early (within 30 days) and late (beyond 30 days) mortality. All-cause mortality is the most robust and unbiased index because no adjudication is required; thus, inaccurate or biased documentation or clinical assessments are avoided [15]. Information about death was obtained from the institutional database and the General Register Office for all patients.

Statistical analysis

For baseline characteristics, variables are summarized as median with relative interquartile range (IQR) for continuous variables and proportion for categorical variables. Multiple imputation was used to address missing data (http://www.jstatsoft.org/v45/i07/). To control for measured potential confounders in the data set, a propensity score (PS) matching was used. PS was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with treatment type (RA versus SV) as a binary dependent variable (http://CRAN.Rproject.org/package=nonrandom). Variables used in the propensity match included: age, gender, BMI, baseline creatinine≥200mmol/l, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), left ventricular ejection fraction (LVEF) ≤49%, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous cerebrovascular accident (CVA), hypertension, current smoking, peripheral vascular disease (PVD), preoperative atrial fibrillation (AF), non-elective surgery, preoperative use of intra-aortic balloon pump (IABP), vessels diseased including diagonal branch (DIA), circumflex artery (CX) and right coronary artery (RCA) and year of operation. Pairs of patients receiving RA and SV were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS. Time segmented Cox regression (within 30 days and beyond 30 days from surgery) was used to investigate the influence of the RA on survival. Second-order interaction between the treatment indicator and BMI (RAvsSV*BMI) in the matched sample was forced in a time segmented Cox model for early (within 30 days) and late hazard phases (beyond 30 days). BMI linearity was assessed using a likelihood ratio test, including age as either a linear term or with a restricted spline fit. The likelihood ratio test showed that the cubic term for BMI yielded a better fit than the linear model (X^2=12; P=0.002). A Schoenfeld residuals test ruled out violation of the proportional hazard assumption (P=0.50). The effect of the RA across BMI values on late mortality was obtained using nonparametric bootstrap covariance analysis for regression coefficients (n = 500 repetitions) (rms R package version 4.2-0: http://CRAN.R-project.org/package=rms). As sensitivity analysis, the effect of the RA on late mortality was tested across BMI categories normal weight (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), obese (BMI, 30-34.9 kg/m^2), and severely obese (BMI ≥ 35 kg/m^2) . All p-values <0.05 were considered to indicate statistical significance. All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The study population consisted of 12244 patients (median age 68 years, IQR 61-74). Of those, 8740 subjects were non-obese (BMI<30, median BMI 26, IQR 24-28) and 3504 obese (BMI≥30, median BMI 32, IQR 31-35). The RA was used in 1322(15%) non-obese patients and 685(20%) obese patients. Number of procedures using the radial artery (RA) or the saphenous vein only (SV) among non-obese (BMI<30) and obese patients (BMI≥30) during the study period are summarized in Figure 1. Mean number of grafts was 2.80±0.70 versus 2.87±0.67 in the RA and SV groups respectively (P<0.001). In the non-obese group, the RA was used to graft the right coronary artery (RCA) in 316(24%) cases and the circumflex artery in 1006(76%) cases. In the obese group, the RA was used to graft the right coronary artery (RCA) in 150(22%) cases and the circumflex artery in 535(78%) cases.

Pre-treatment variables distributions in RA group and in unmatched and PS-matched SV groups are summarized in Table 1. Before PS matching the two groups were not comparable for all but four of pre-treatment variables. PS matching selected 2007 SV patients with pre-treatment variables distributions similar to those in the RA group including both BMI categories as well as mean number of grafts (2.80±0.70 versus 2.81±0.70 in the RA and SV groups respectively; P=0.65).

Effect of the RA on early and late survival

In the RA group there were 8(0.4%) early deaths (within 30 days) compared to 160(1.6%) in the unmatched SV group ($HR_{early\ phase}$ 0.25; 95%CI 0.12-0.51; P<0.001) and 18(0.9%) in the PS-matched SV group ($HR_{early\ phase}$ 0.44; 95%CI 0.19-1.02; P=0.06). After a median follow-up time of 7.5 years (IQR 3.6-11.3), survival probability at 5, 10 and 15 years in the RA group were 93.8%±0.6%, 84.2%±0.9% and 69.4%±1.9% compared to 87.7%±0.3%, 70.9%±0.5% and 51.4%±0.08% in the unmatched SV group ($HR_{late\ phase}$ 0.54; 95%CI 0.48-0.60; P<0.0001, Figure 2, left) and 90.9%± 0.7%, 79.5%±1.1% and 63.9%±1.6% in the PS-matched SV group ($HR_{late\ phase}$ 0.86; 95%CI 0.74-0.99;P=0.04, Figure 2, right).

Impact of body mass index on mortality

BMI did not modify the effect of the RA on early mortality (interaction P=0.43) but there was a significant interaction between BMI and the use of the RA over SV on late mortality (interaction P=0.02). In particular, the survival advantage conferred by the RA gradually declined with increasing patient's BMI and it was no longer statistically significant above a BMI >29 (Figure 3). The use of the RA reduced the risk of late death in subjects with BMI<30 ($HR_{late\ phase}$ 0.78; 95%CI 0.65-0.94; P=0.008; Figure 4, left) but not in those with BMI≥30 ($HR_{late\ phase}$ 1.05; 95%CI 0.80-1.38; P=0.72; Figure 4, right). Finally we found a significant interaction between diabetes and effect of the

RA in non-obese patients with a larger benefit among non-diabetics ($HR_{late\ phase}$ 0.69[0.56-0.85]) when compared to diabetics ($HR_{late\ phase}$ 0.81[0.45-0.99], interaction P=0.01). However, we could not demonstrated a significant survival benefit in obese patients regardless of their diabetes status (non-diabetic $HR_{late\ phase}$ 0.87[0.63-1.20] versus diabetics $HR_{late\ phase}$ 0.83[0.54-1.26]; interaction P=0.8).

Discussion

The main finding of the present study is that the use of the RA in preference to SV as second conduit was associated with improved long term survival in non-obese patient undergoing CABG. The RA-related benefit was more pronounced in the absence of diabetes. However, this benefit was no longer present in obese patients regardless of their diabetes status.

In recent years, the obesity epidemic is growing both in the general population [1] and in patients undergoing CABG [2,3]. Obesity has been associated with poorer long term outcomes, after CABG, explained by the accelerated atherosclerotic graft progression [4,5]. The use of additional arterial conduits to the standard left internal thoracic artery has been advocated to improve survival after CABG given the up to 50% failure of SV grafts graft at 10 years post-surgery [16]. The RA is often preferred over the second internal thoracic artery in obese patients to reduce the potential sternal wound complication [7,8]. However, obesity has been reported to promote RA vasoreactivity and early inflammation, myointimal hyperplasia and atherosclerotic degeneration in other clinical settings [10-14] and these observations raise concern on the efficacy of the RA as a second arterial graft in this population.

Obese patients have high levels of serum hs-CRP, which is known to trigger myointimal hyperplasia and a higher tendency of atheroma and calcification of the RA [11], suggesting the possibility of pre-existing vascular disease in those patients.

Moreover adiponectin, an adipocyte-derived collagen-like protein is decreased in obesity and this has been suggested to promote the production of adhesion molecules in endothelial cells, proliferation of smooth muscle cells and endothelial dysfunction [10], increased neo-intimal hyperplasia and atherosclerosis changes in the RA of obese adults [17].

No previous study has investigated the influence of obesity on survival in patients undergoing CABG using the RA as second conduit in preference to SV grafts. In the present analysis we demonstrated that the survival advantage in non-obese patients by using the RA is no longer present in obese patients regardless their diabetic status. In a previous study we found that the use of bilateral internal thoracic arteries improves survival in obese patients undergoing CABG when compared to the conventional strategy with a single internal thoracic artery [6]. It can be speculated that compared to the RA, internal thoracic arteries might be more resistant to atherosclerosis in obese subjects thus achieving a better patency rate because of their capacity to release nitric oxide [18,19].

The present study has some limitations. The study was observational on prospectively collected data which cannot exclude the role of selection bias. Propensity technique can adjust only for measurable and included variables and we cannot exclude a selection bias based on non-measurable "eye-ball" variables (with the RA reserved to healthier and better patients). We did not measure the changes in the BMI during the follow-up period; hence, no causality of the interrelationship between these parameters could be determined. In addition, obesity was defined only by the BMI in the present study, rather than by an actual measure of adiposity, such as the waist circumference. However, the BMI is a widely available, simple, and practical measurement of obesity, and numerous studies have used BMI as a surrogate measure of adiposity [20]. The long period of enrolment could theoretically have affected the preference of radial artery as a possible conduit. As shown in Figure 1 the rate of RA usage did not vary remarkably during the years and we have included the era of surgery in the PS model to account for this confounding factor. However, we cannot exclude residual patient selection bias. Finally, no follow-up data were available to compare the groups with respect to the cause of death (cardiac vs noncardiac), recurrence of angina, need for repeated revascularization, and graft patency. Therefore we can only speculate that the mechanism beyond differences in survival rate observed among the groups is related to the differences in patency rates of the RA over the SV.

In conclusion, the survival benefit conferred by the use of the RA in preference to SV, among non-obese patients undergoing CABG, was no longer present in obese patients regardless of their diabetic status. Further studies are warranted to determine the pathophysiology underlying this observation and to identify which subgroup of obese patients is more likely to benefit from the use of the RA.

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Table 1. Pre-treatment variable distribution in the radial artery (RA) group and in the unmatched (um) and propensity score matched (m) saphenous vein (SV) group

	RA group N=2007		Um-SV group N=10237		P	m-SV group N=2007		P
	N	%	N	%		N	%	
Age <60 yrs	865	43	1651	16	<0.001	879	44	0.62
60.0-69	800	40	3908	38		798	40	
70-79	308	15	4085	40		303	15	
≥80	34	2	593	6		27	1	
Female	267	13	1897	19	<0.001	290	14	0.31
BMI <18.5	6	0	100	1	<0.001	16	1	0.67
18.5-24.9	399	20	2594	25		410	20	
25.0-29.9	917	46	4724	46		880	44	
30.0-34.9	524	26	2201	22		516	26	
≥35.0	161	8.0	618	6		185	9	
MI	900	45	5172	51	<0.001	926	46	0.42
PCI	109	5	568	6	0.87	122	6	0.41
DM	358	18	1974	19	0.14	394	20	0.15
Hypertension	1368	68	7499	73	<0.001	1365	68	0.94
Smoking	315	16	1231	12	<0.001	345	17	0.21
Creatinine≥200mmol	12	1	321	3	<0.001	18	1	0.36
COPD	181	9	1217	12	<0.001	184	9	0.91
CVA	114	6	912	9	<0.001	121	6	0.68
PVD	148	7	1164	11	<0.001	161	8	0.47
AF	53	2	396	4	0.01	54	3	1
LVEF <.50	409	20	2920	29	<0.001	433	22	0.37
Preoperative IABP	12	1	197	2	<0.001	9	0	0.66
Non elective	819	41	4992	49	<0.001	837	42	0.58
RCA	1300	65	7290	71	<0.001	1234	62	0.06
CX	1625	81	8318	81	0.78	1620	81	0.87
DIA	484	24	2256	22	0.04	498	25	0.63
LMD	495	25	2729	27	0.07	489	24	0.85
YOP 1996-2004	905	45	4285	42	<0.001	913	46	0.06
2005-2015	1102	55	5952	58		1094	55	0.06

BMI: body mass index; MI: myocardial infarction; PCI: percutaneous coronary intervention; DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PVD: peripheral vascular disease; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; IABP: intra-aortic balloon pump; RCA: right coronary artery; CX: circumflex; DIA: diagonal; LMD: left main disease; YOP: year of operation

Figure Legend

Figure 1. Number of procedures using the radial artery (RA) or the saphenous vein only (SV) among non-obese (BMI<30) and obese patients (BMI≥30) during the study period.

Figure 2. Survival curves for patients receiving the radial artery (RA) and saphenous vein (SV) in the unmatched and propensity score matched samples.

Figure 3. Non parametric bootstrap 95% confidence limits set for the radial artery (RA) versus saphenous vein (SV) grafting hazard ratios for a variety of body mass index (BMI) on late (beyond 30 days) mortality

Figure 4. Survival curves for patients receiving the radial artery (RA) and saphenous vein (SV) in propensity score matched non-obese and obese patients